

REMARKS

A check for the fee for a three (3) month extension of time and for a Petition under 1.48(b) accompanies this response. Any fees that may be due in connection with filing this paper or with this application may be charged to Deposit Account No. **06-1050**. If a Petition for extension of time is needed, this paper is to be considered such Petition.

As noted in the previous response, cancellation of the claims required a consideration of inventorship. Cancellation of claims in the application requires deletion of inventors of the application. The inventive entity in the application is changed from Daniel J. Von Seggern, Glen R. Nemerow, Paul Hallenbeck, Susan Stevenson and Yelena Skripchenko to an inventive entity of Daniel J. Von Seggern and Glen R. Nemerow. A Petition under 37 C.F.R. §1.48(b) is filed herewith pursuant to the change in inventive entity.

Claims 1, 2, 4-23, 41, 47, 69 and 95-103, are presently pending in this application. Claims 5, 10, 14, 19 and 101 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form, including all of the limitations of the base claim and any intervening claims. It is acknowledged that the prior art does not teach or suggest SEQ ID NO. 32, SEQ ID NO. 43, SEQ ID NO. 44, SEQ ID NO. 47, SEQ ID NO. 64, SEQ ID NO. 65, SEQ ID NO. 26 or SEQ ID NO. 8.

It is respectfully submitted that Claim 5 as amended in the Preliminary Amendment and CPA filed April 14, 2003, is in independent form and therefore allowable. With respect to the remaining claims, Applicant wishes to defer amendment to independent form, pending a determination of allowability of the claims from which they depend.

Claims 1, 2, 6-8, 13, 14, 16-20, 47, 69, 97-99, 102 and 103 are amended herein. Claims 1, 2 and 6 are amended to clarify that the nucleic acid molecules contain TPL exons such that at least two of the different exons are

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not normally found together in nature, *i.e.*, they are from different viruses and/or in a non-native order or both. As discussed below, the amendments find basis, for example, at page 28, lines 27-30; page 34, lines 23-25; page 35, lines 26-28; page 36, lines 17-19 and 21-23; and Example 5 at page 93, lines 17-19 of the specification.

Claim 6 is amended to replace "partial exon 1" with —partial TPL exon 1— to clarify that the exon is a TPL exon. Claim 97 is amended to replace "the stably integrated" with —a stably integrated— for grammatical clarity. Claims 7, 8, 13, 14, 16-20, 69, 98 and 99 are amended to insert a comma or commas for proper claim punctuation. Claim 13 is further amended to replace "first TPL exon" with —TPL exon 1—, to provide proper antecedent basis in Claim 12, from which it depends. The amendment finds basis in Claim 12. Claim 19 is further amended to insert the inadvertently omitted verb "selected" for grammatical clarity.

Claim 47 is amended to clarify that the claim is directed to the method of claim 41, wherein the adenovirus structural protein is adenovirus fiber protein and to provide proper antecedent basis in Claim 41. Claims 102 and 103 are amended to correct minor spelling errors. No new matter has been added to the claims.

Provided herewith is a Petition pursuant to 37 C.F.R. §1.48(b) to change inventorship of the above-captioned application to Daniel J. Von Seggern and Glen R. Nemerow. This change in inventorship is necessitated by cancellation of claims from the application in the Preliminary Amendment filed with a Continued Prosecution Application (CPA) on April 14, 2003, in connection with the above-captioned application. Applicant notes that the change in inventorship renders inventorship of the instant application identical to that of the priority document, Nemerow *et al.* (International PCT publication WO 98/13499 corresponding to priority document International Application

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PCT/EP97/05251). Therefore, the inventive entity of Nemerow *et al.* is the same as the inventive entity of this application.

A Supplemental Information Disclosure Statement is being filed on the same day herewith under separate cover.

The specification is amended to clarify the language of the priority claim; no change in the priority claim is requested. Hence, priority is claimed to U.S. Application No. 09/423,783, International Application No. PCT/EP97/05251, filed September 24, 1997, U.S. Application No. 08/719,806, filed September 25, 1996, now abandoned, and U.S. Application No. 09/795,292, converted to a U.S. Non-Provisional Application from U.S. Provisional Application No. 60/115,920, filed January 14, 1999.

PRIORITY

1) Priority Documents U.S. Application No. 08/719,806 and International Application PCT/EP97/05251

The Examiner has assessed the priority status of the pending claims and states that the subject matter for which support is found in the plasmid pCLF disclosed in the above applications includes: when the TPL exons are different, *i.e.*, TPL 1, 2, 3, but from the same adenovirus. The Examiner alleges that the subject matter directed to: same TPL exons, or different TPL exons from the same or different adenoviruses that are in non-native order finds basis only in the instant application and not in the above-mentioned priority applications. The Examiner further states that should Applicant disagree with the above factual determination, it is "incumbent" upon Applicant to provide the serial number and specific page number(s) of any parent application that specifically supports the particular claim.

It is respectfully submitted that, barring the citation of any intervening art, it is not "incumbent" upon Applicant to provide the priority basis of the pending claims. The only time basis is required is where intervening art is cited. In this

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instance, the only intervening art cited is Curiel (US 5,871,727; filing date December 6, 1996). Of the pending claims, Claims 100-102 find basis in plasmid pCLF disclosed in the above priority documents and are accorded a priority date of September 25, 1996. Curiel is not prior art with respect to claims 100-102 and has not been cited as such.

2) Priority Document U.S. Application No. 09/795,292

The Examiner states that because Application No. 09/795,292 is not available for consideration at the present time, there is no way to determine whether the instantly claimed subject matter would find support in the '292 application. The Examiner further requests that Applicant provide specific basis in the '292 application, if any, for the pending claims.

The only time basis is required is where intervening art is cited. In this instance, as discussed above, the only intervening art cited is Curiel, which is prior art to the '292 application. Thus, pointing to basis in the '292 application for any of the claims rejected over Curiel will not remove Curiel as prior art. Furthermore, Applicant is arguing the propriety of the rejection below. Thus, there is no need to provide basis for any of the rejected claims in the '292, since the rejection should be withdrawn on the merits and finding basis in the '292 application does not obviate Curiel as prior art. Similarly, any other art cited predates the date of the earliest priority document.

Moreover, as discussed below under "Information Disclosure Statement," a telephonic inquiry regarding the issue of availability of the '292 application was made to Examiner Foley on December 2, 2003, and the Examiner indicated that the '292 application, while not available for review at the time the instant Office Action was mailed, may be considered later if Applicant again provides the Application Serial Number and filing date in a subsequent Information Disclosure Statement filed on the same day herewith. Applicant therefore

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respectfully requests consideration and entry of the '292 priority document into the file history of the above-captioned application.

INFORMATION DISCLOSURE STATEMENT

The Office Action reports that the Examiner lined through several of the U.S. applications listed by the Applicant in the Information Disclosure Statement filed April 18, 2003. The Examiner states that either the application numbers could not be determined or the applications were not available. Three U.S. applications were apparently not considered by the Examiner because U.S. Application Serial Numbers were not available at the time the Information Disclosure Statement of April 18, 2003, was filed. Serial numbers for two of the applications, U.S. Application Serial No. 10/403,337 and U.S. Provisional Application Serial No. 60/459,000, were provided in a Supplemental Information Disclosure Statement filed May 22, 2003.

For convenience, the now available U.S. Application Serial Numbers and filing dates for each U.S. application are listed in the Information Disclosure Statement filed on the same day herewith. The remaining application that was not considered is U.S. application Serial No. 09/795,292, of which the instant application is a continuation-in-part. A telephonic inquiry regarding this issue was made to Examiner Foley on December 2, 2003. The Examiner indicated that U.S. application Serial No. 09/795,292, was not available for review at the time the instant Office Action was mailed, but would be considered if Applicant again provides the application serial number and filing date in a subsequent Information Disclosure Statement. In response, Applicant provides this information in the Supplemental Information Disclosure Statement filed on the same day herewith.

**REJECTION OF CLAIMS 9, 18, 100, 102 and 103 UNDER 35 U.S.C. §112,
FIRST PARAGRAPH**

Claims 9, 18, 100, 102 and 103 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one of skill in the art to make and/or use the subject matter of the claims. The Office Action states that plasmids pCLF, pDV60, pDV67, pDV69, pDV80 and pDV90 are required elements of the claims and as such must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. The Office Action further states that deposit of the plasmids may satisfy the enablement requirement.

The Office Action alleges that the specification does not provide a repeatable method for obtaining the claimed plasmids and that Applicant's deposit statement bridging pages 88 and 89 of the specification does not indicate the extent of public availability of the claimed plasmids. The Office Action states that if the deposits were made under the terms of the Budapest Treaty, a statement by the appropriate party that the deposits have been made under the terms of the Budapest Treaty and all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, would satisfy the deposit requirements. Reconsideration of the grounds for this rejection is respectfully requested in view of the following remarks.

Deposit of biological materials is not necessary if the materials, or starting materials, are known and readily available to the public, or obtainable by a repeatable method set forth in the specification. For plasmids pCLF, pDV60, pDV67, pDV69, pDV80 and pDV90, the complete nucleotide sequences are provided in the sequence listing as SEQ ID NOs. 8, 43, 44, 47, 64 and 65, respectively. Therefore, given the availability of the nucleotide sequence of

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each plasmid, one of skill in the art can readily make and/or use the claimed subject matter.

In addition to providing the complete nucleotide sequences of each plasmid, the specification sets forth detailed protocols for obtaining each plasmid from readily available starting materials (see Example 1, beginning on page 63 for construction of pCLF; Example 6, beginning on page 94, for construction of pDV60, pDV67 and pDV69; Example 10, beginning on page 107, for construction of pDV80; and Example 11, beginning on page 110, for construction of pDV90).

Thus, given the availability of the nucleic acid sequences, as well as detailed methods for arriving at such nucleic acid sequences, one of skill in the art can readily make and/or use the instantly claimed plasmids and a deposit is not necessary. Thus, Applicant respectfully submits that, as discussed above, deposited plasmids are not required for one of skill in the art to make and/or use the claimed subject matter.

REJECTION OF CLAIMS 1 and 11 UNDER 35 U.S.C. §102(b)

Claims 1 and 11 are rejected under 35 U.S.C. §102(b) as being anticipated by Logan *et al.*, or in the alternative, by Sheay *et al.*

The Office Action alleges that Logan *et al.* discloses plasmid pJAW43, which allegedly encodes TPL sequences from Ad2, and plasmid pE1A-WT, which allegedly encodes rearranged E1A genes and 5' tripartite leader segments. The Office Action alleges that Sheay *et al.* discloses plasmid pRD112a, which encodes Ad2 TPL sequences.

The Examiner contends that Applicant's arguments in the previous Amendment of April 14, 2003, indicating that "different" TPL exons means the TPL exons are "not normally found together in nature", are unpersuasive. The Examiner alleges that the cited passage encompassing "not normally found together in nature" (page 34, lines 23-25) refers to generic recombinant DNA

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molecules and not TPL exons. The Examiner further contends that Applicant's earlier definition of "different" as being "not the same," provided in the Amendment filed December 19, 2001, means that the "different" TPL exons could either be from different adenoviruses or different TPL exons from the same adenovirus. The Examiner concludes that, based on the "clarification" provided in the Amendment filed December 19, 2001, the TPL exons of Logan *et al.* and Sheay *et al.* are "different" by virtue of being different exons from the same adenovirus and therefore these references anticipate Claims 1 and 11. Reconsideration and withdrawal of this rejection are respectfully requested in view of the clarifying amendments herein and the following remarks.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir. 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundsciber Corp. v. U.S., 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl. 1966). See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference In re Oelrich, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

CLAIMS

Claim 1 as amended herein is directed to an isolated nucleic acid molecule containing a sequence of nucleotides encoding an adenovirus tripartite leader (TPL), wherein the TPL-encoding sequence of nucleotides comprises: (a) first and second different TPL exons, , wherein the different TPL exons are from different adenoviruses, or in a non-native order or both, or (b) first, second and third same or different TPL exons, wherein at least two of the different TPL exons are from different adenoviruses, or in a non-native order or both, wherein said TPL exons are selected from the group consisting of complete TPL exon 1, complete TPL exon 2 and complete TPL exon 3. (emphasis added) Dependent Claim 11 is directed to a plasmid that contains the nucleic acid molecule of claim 1. Thus, Claims 1 and 11 as amended herein specify that at least two of the "different" TPL exons that are an element of these claims are from different adenoviruses, or in a non-native order or both.

Differences between the disclosure of Logan *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* 81:3655-3659 (1994)) and Claims 1 and 11

Logan *et al.* discloses nucleic acid molecules including tripartite leader sequences from adenovirus type 2. Specifically, Logan *et al.* discloses constructs, such as plasmid pE1A-WT, which contain the adenovirus type 2 TPL exons in their native order with one or more of the TPL exons being "partial." Logan *et al.* does not disclose any isolated nucleic acid molecules containing TPL sequences in which at least two of the TPL exons are either (1) the same; or (2) from different adenoviruses, or (3) from the same adenovirus but in non-native order. Therefore, Logan *et al.* does not anticipate Claims 1 and 11, which specify that at least two TPL exons are either the same, or if they are different, they are from different adenoviruses or in a non-native order.

Rebuttal to Examiner's Arguments

The Examiner alleges that Applicant's arguments in the previous Amendment of April 14, 2003, indicating that "different" TPL exons means the TPL exons are "not normally found together in nature", are unpersuasive. The Examiner alleges that the cited passage encompassing "not normally found together in nature" (page 34, lines 23-25) refers to generic recombinant DNA molecules and not TPL exons. The Examiner further contends that Applicant's earlier definition of "different" as being "not the same," provided in the Amendment filed December 19, 2001, means that the "different" TPL exons could either be from different adenoviruses or different TPL exons from the same adenovirus. The Examiner concludes that, based on the "clarification" provided in the Amendment filed December 19, 2001, the TPL exons of Logan *et al.* and Sheay *et al.* can be "different" by virtue of being different exons from the same adenovirus and therefore these references anticipate Claims 1 and 11.

As discussed below, Applicant respectfully submits that the rejected claims as amended herein clarify the meaning of the term "different" in the context of these claims as directed to operatively linked TPL exons from different viruses and/or TPL exons that are in non-native order. As discussed below and as acknowledged by the Examiner at page 3 of the Office Action, there is basis throughout the specification for the claims as amended herein. Further, contrary to the Examiner's assertion, there is basis in the specification for isolated TPL sequences containing operatively linked "different" TPL exons that are "not normally found together in nature."

A. The rejected claims as amended herein specify that when the TPL exons are different, at least two different TPL exons are from different adenoviruses or in non-native order, or both.

As the Examiner has acknowledged at page 3 of the instant Office Action, and as discussed below, there is basis in the specification for isolated nucleic acid molecules containing TPL sequences that are "different" and either

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from (1) the same adenovirus; or (2) from different adenoviruses; or (3) that are present in non-native order ("mixed-up," *see* page 3). Specifically, the Examiner points to page 36, lines 12-20, and to Examples 5 and 6, beginning on page 92 of the specification, as providing basis for the aforementioned combinations of TPL exons. The rejected claims (1 and 11, and Claims 2 and 4, discussed below) as amended herein specify that at least two of the "different" TPL exons are from category (2) or category (3) or both.

When the TPL exons are "different", they may come from either the same adenovirus or different adenoviruses and can further be operatively linked in a variety of configurations (*see, e.g.*, page 36, lines 17-19 and 21-23, which describe that the TPL exons may be derived from any adenovirus serotype and can be operatively linked in a variety of configurations that may or may not include an operatively linked intron sequence; *see also* page 28, lines 27-30, that provides that the disclosed recombinant DNA sequences may be prepared using nucleic acid sequences derived from different Ad serotypes, in order to design useful constructs with broad applicability; *see also* Example 5 at page 93, lines 17-19, describing that TPL fragments containing two of the three exons or exons in non-native order may be constructed for use in preparing complementing plasmids).

The specification further discloses that the recombinant DNA sequences, including TPL sequences, of the instant application can be generated from any adenovirus serotype (*see* page 28, lines 27-28 and page 36, lines 17-19). Furthermore, Example 5, beginning on page 92 of the specification, provides basis for any combination of TPL sequences, including sequences comprising 2 or 3 TPL exons, TPL exons in non-native order, and TPL sequences with or without an intron (*see, e.g.*, page 93, lines 17-19). The specification further recites that amplified TPL exons can be "ligated together in any desired number and/or order" (*see* page 93, line 30).

Therefore, there is basis in the specification for the claims as amended herein that specify that when the TPL exons are different, at least two of the different TPL exons are from different adenoviruses or in non-native order, or both.

B. Contrary to the Examiner's assertion, there is basis in the specification for TPL sequences falling within the scope of generic recombinant nucleic acid molecules containing sequences "not normally found together in nature."

Contrary to the Examiner's assertion and as discussed below, there is basis throughout the specification for isolated TPL sequences containing operatively linked TPL exons as falling within the scope of recombinant nucleic acid molecules containing operatively linked sequences (*e.g.*, TPL exons in the case of TPL sequences) that are "not normally found together in nature."

When the TPL exons are the same or when "different" TPL exons are combined from different adenoviruses or in a desired configuration that is not that of the native adenovirus sequence (non-native order), the nucleotide sequences containing the operatively linked TPL exons can be prepared by recombinant techniques. As the specification describes, *e.g.*, at page 23, lines 11-13, the isolated DNA molecules provided in the specification, which would include the isolated TPL sequences discussed above, may be single-stranded or double-stranded, and may be genomic DNA, cDNA, recombinant hybrid DNA, or synthetic DNA (emphasis added). As the specification further provides, *e.g.*, at page 34, lines 23-25, a recombinant DNA molecule as instantly claimed is a hybrid DNA molecule comprising at least 2 nucleotide sequences not normally found together in nature (emphasis added). The specification then goes on to describe the various nucleotide sequences that form part of the instantly claimed subject matter, including TPL sequences, and, when desired, their recombinant assembly (see page 35, line 3 to page 37, line 14; see *also* page 34, lines 9-11 describing that nucleotide sequences disclosed and claimed herein include sequences of "enhancer elements," *i.e.*, TPL sequences). Therefore, contrary to

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the Examiner's assertion, there is ample basis throughout the specification for the instantly claimed isolated nucleic acid molecules containing TPL sequences that can recombinantly assembled using "different" TPL exons that are within the scope of recombinant nucleic acid molecules containing operatively linked sequences that are not normally found together in nature.

The specification describes several types of isolated nucleic acid molecules as falling within the scope of recombinant DNA molecules. The specification states that "A subject nucleotide sequence consists of a nucleic acid molecule that comprises at least 2 different operatively linked DNA segments" (see page 34, lines 12-13). One such example provided in the specification of two operatively linked DNA segments of the instant application are the TPL sequences as set forth in Claims 1 and 11, "Thus, the invention contemplates a nucleic acid molecule comprising a TPL nucleotide sequence" (see page 35, lines 19-20). Applicant respectfully submits that the TPL sequences of the instant application do fall within the scope of recombinant DNA molecules described in the specification and as such comprise at least two nucleotide sequences "not normally found together in nature", *i.e.*, TPL sequences containing operatively linked TPL exons from different adenoviruses and/or linked in a non-native order.

Because the instant application provides basis for TPL sequences containing the same TPL exons or different TPL exons such that at least two different TPL exons are from different adenoviruses and/or in non-native order or both, and because such TPL sequences are an element of Claims 1 and 11, Logan *et al.*, which does not disclose TPL sequences containing operatively linked same TPL exons or different TPL exons from different adenoviruses and/or in non-native order or both, does not anticipate the claims.

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Differences between the disclosure of Sheay *et al.* (*Biotechniques* 15(5):856-862 (1993)) and Claims 1 and 11

Sheay *et al.* discloses nucleic acid molecules including tripartite leader sequences from adenovirus type 2. Specifically, Sheay *et al.* discloses plasmid pRD112a, which encodes TPL exons 1, 2 and 3 from Ad2. Sheay *et al.* does not disclose any isolated nucleic acid molecules containing TPL sequences containing TPL exons that are either the same or where at least two of the TPL exons are from different adenoviruses and/or in a non-native order. As discussed above, there is basis for the claims as amended herein, specifying that when the operatively linked TPL exons in the isolated TPL sequence are "different," they are from different adenoviruses and/or in a non-native order, *i.e.*, not normally found together in nature. Because Sheay *et al.* does not disclose any isolated TPL sequences containing operatively linked "same" TPL exons or different TPL exons that are from different adenoviruses and/or in a non-native order, Sheay *et al.* does not anticipate Claims 1 and 11.

Because neither Logan *et al.* nor Sheay *et al.* disclose or suggest any isolated TPL sequences in which at least two of the TPL exons are the same or different but from different adenoviruses and/or in a non-native order, neither reference discloses all the elements of Claims 1 and 11. Therefore, since anticipation requires that a reference disclose all elements as claimed, Logan *et al.* and Sheay *et al.* do not anticipate Claim 1 or Claim 11.

REJECTION OF CLAIMS 1, 2, 4 and 11 UNDER 35 U.S.C. §102(b)

Claims 1, 2, 4 and 11 are rejected under 35 U.S.C. §102(b) as being anticipated by Kaufman because Kaufman allegedly discloses plasmid pD20, which contains the 2nd and 3rd TPL exon sequences and the 5' splice site from the adenovirus first late leader sequence. The Office Action further alleges that Kaufman discloses plasmid pD15, which contains the same sequences as pD20, but the exons are in opposite orientation with respect to the direction of

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transcription. Kaufman is further alleged to disclose plasmids containing the entire adenovirus TPL sequence ("Plasmid Construction" bridging pages 689-690 and Figure 1). Reconsideration of these grounds for rejection is respectfully requested in view of the clarifying amendments herein and the following remarks.

RELEVANT LAW

See above.

CLAIMS

Claims 1 and 11 are discussed above.

Claim 2 is directed to is directed to an isolated nucleic acid molecule containing a sequence of nucleotides encoding an adenovirus tripartite leader (TPL), wherein the TPL-encoding sequence of nucleotides comprises: (a) first and second different TPL exons, wherein the different TPL exons are from different adenoviruses, or in a non-native order or both or (b) first, second and third same or different TPL exons, wherein at least two of the different TPL exons are from different adenoviruses, or in a non-native order or both, said TPL exons selected from the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3, wherein the sequence of nucleotides encoding a TPL is operatively linked to an intron containing an RNA processing signal. Dependent Claim 4 specifies that the intron is native adenovirus intron 1.

Differences between the disclosure of Kaufman (*Proc. Natl. Acad. Sci. U.S.A.* 82:689-693 (1985)) and Claims 1, 2 and 4 and 11

Kaufman discloses nucleic acid molecules containing TPL sequences from Ad2 and a hybrid intron formed by the 5' splice site of the adenovirus first late leader and the 3' splice site of an immunoglobulin variable-region gene. Specifically, Kaufman discloses plasmids pD15 and pD20, which are derived from plasmids pJAW43 (discussed above with the disclosure of Logan *et al.*)

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and pAdD26SVp(A)3. Plasmid pAdD26SVp(A)3 contains (a) the cDNA sequence of the mouse DHFR gene under the control of the adenovirus major late promoter, (b) TPL exon 1 and (c) a hybrid intron formed by the 5' splice site of the adenovirus first late leader and the 3' splice site from a variable region immunoglobulin gene. Plasmids pD15 and pD20 are identical to plasmid pAdD26SVp(A)3 except that they contain a 138 bp insertion encoding TPL exon 2 and partial TPL exon 3 from plasmid pJAW43. Plasmids pD15 and pD20 differ from each other only by the orientation of the 138 bp insertion with respect to the direction of transcription. Therefore, Kaufman discloses constructs containing portions of Ad2 TPL sequences and a hybrid intron. Contrary to the Examiner's assertion, the constructs disclosed by Kaufman (unlike the pJAW43 plasmid from which they are derived) do not contain the entire adenovirus TPL sequence, but complete exons 1 and 2 and a portion of exon 3.

Kaufman does not disclose any isolated nucleic acid molecules containing TPL sequences in which at least two of the different TPL exons are from different adenoviruses or in non-native order or both, *i.e.*, not normally found together in nature. Kaufman also does not disclose any isolated nucleic acid molecules containing TPL sequences in which the TPL exons are the same exon (*e.g.* TPL exon 2 and TPL exon 2) from either the same adenovirus or from different adenoviruses, or any other combination of TPL exons that are not normally found together in nature (*e.g.*, TPL exon 1 and TPL exon 3, from the same or different adenoviruses, without TPL exon 2 intervening). Furthermore, unlike Claim 4, Kaufman does not disclose any isolated nucleic acid molecules containing TPL sequences operatively linked to native adenovirus intron 1.

Claims 1, 2, 4 and 11 specify that at least two of the "different" TPL exons are from different adenoviruses or in non-native order or both. As discussed above, there is basis throughout the specification for recombinant TPL

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sequences containing various combinations of TPL exons, including those from different adenoviruses or in non-native order or both. Kaufman does not disclose any combinations of TPL exons from different viruses and/or in non-native order.

Further, contrary to the Examiner's assertion, Kaufman does not disclose any isolated nucleic acid sequences containing TPL sequences operatively linked to native adenovirus intron 1. The intron contained in plasmids pAdD26SVp(A)3, pD15 and pD20 is a hybrid intron created by the 5' splice site of the adenovirus first late leader and the 3' splice site from a variable region immunoglobulin gene (see Kaufman and Sharp, *Mol. Cell. Biol.* 2(11):1304-1319 (1982) for details on the components of plasmid pAdD26SVp(A)3; Kaufman and Sharp is being provided in an Information Disclosure Statement filed on the same day herewith). As is known to those of ordinary skill in the art, an intron is defined by specific sequences at the 5' and 3' splice sites. Therefore, the intron disclosed by Kaufman is not the same as native adenovirus intron 1 and thus, Kaufman does not anticipate Claim 4.

Because Kaufman does not disclose any isolated TPL sequences in which at least two of the different TPL exons are from different adenoviruses and/or in non-native order, Kaufman does not disclose every element of Claims 1, 2, 4 and 11 and therefore does not anticipate these claims. Further, unlike Claim 4, Kaufman does not disclose isolated nucleic acid molecules containing TPL sequences operatively linked to native adenovirus intron 1. Therefore, since anticipation requires that a reference disclose all elements as claimed, Kaufman does not anticipate Claims 1, 2, 4 or 11.

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REJECTION OF CLAIMS 6-8 UNDER 35 U.S.C. §103(a)

Claims 6-8 are rejected under 35 U.S.C. §103(a) as being unpatentable over Sheay *et al.*, or alternatively over Kaufman, in view of Curiel (US 5,871,727). The Office Action alleges Sheay *et al.* and Kaufman teach adenovirus TPL sequences and Curiel teaches a plasmid comprising a chimeric fiber gene encoding the Ad5 tail and Ad3 head. The Office Action concludes that it would have been obvious to one of ordinary skill in the art at the time the instant application was filed to combine the TPL sequences of Sheay *et al.* or Kaufman with the chimeric adenovirus fiber gene of Curiel to arrive at the instantly claimed subject matter. This rejection is respectfully traversed.

RELEVANT LAW

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. §103: (1) there must be some teaching, suggestion or incentive supporting the combination of cited references to produce the claimed invention (ACS Hosp. Systems, Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)) and (2) the combination of the cited references must actually teach or suggest the claimed invention. Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. Ex parte Gerlach, 212 USPQ 471 (Bd. App. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art." In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (ACS Hosp. Systems, Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight

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syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

Further, that which is within the capabilities of one skilled in the art is not synonymous with that which is obvious. *Ex parte Gerlach*, 212 USPQ 471 (Bd. APP. 1980). Obviousness is tested by "what the combined teachings of the references would have suggested to those of ordinary skill in the art" *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981), but it cannot be established by combining the teachings of the prior art to produce the claimed subject matter, absent some teaching or suggestion supporting the combination (*ACS Hosp. Systems, Inc. v Montefiore Hosp.* 732 F.2d 1572, 1577. 221 USPQ 929, 933 (Fed. Cir. 1984)). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" *W.L. Gore & Associates, Inc. v Garlock Inc.*, 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

CLAIMS

Claim 6 is directed to an isolated nucleic acid molecule containing an adenovirus tripartite leader (TPL) nucleotide sequence, said TPL nucleotide sequence comprising (a) first and second different TPL exons, wherein the different TPL exons are from different adenoviruses, or in a non-native order or both or (b) first, second and third same or different TPL exons, wherein at least two of the different TPL exons are from different adenoviruses, or in a non-native order or both, said TPL exons selected from the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3 and further comprising a promoter and a sequence of nucleotides that encodes an adenoviral structural protein, operatively linked to said promoter

and said TPL-encoding sequence of nucleotides. Dependent claim 7 specifies that the adenoviral structural protein is a fiber protein or a chimeric fiber protein including a fiber tail domain. Dependent claim 8 further specifies that the chimeric protein of claim 7 comprises an Ad3 head domain and an Ad5 tail domain or an Ad5 head domain and an Ad3 tail domain.

Differences Between the Claims and the Teachings of the Cited References

Sheay *et al.* and Kaufman

Sheay *et al.* and Kaufman are discussed above. Sheay *et al.* and Kaufman are directed to the study of the role of TPL sequences in enhancing gene expression. Sheay *et al.* and Kaufman teach various constructs containing complete TPL exons or portions thereof, linked to an intron sequence (Kaufman) and further to reporter genes (*e.g.*, chloramphenicol acetyl transferase (CAT) in Sheay *et al.*; dihydrofolate reductase (DHFR) and γ -interferon in Kaufman). Sheay *et al.* and Kaufman teach that TPL sequences play a role in enhancing translation when linked to exogenous, non-adenoviral genes. Neither Sheay *et al.* nor Kaufman teaches or suggests operatively linking adenovirus TPL sequences to a promoter or an adenovirus structural protein. Further, as discussed above, neither Sheay *et al.* nor Kaufman teaches or suggests any isolated TPL sequences containing TPL exons that are either the same or are from different adenoviruses and/or in a non-native order.

Curiel (US 5,871,727)

Curiel teaches a genetic technique, using two plasmids, for generation of recombinant adenovirus vectors with modified tropisms. Specifically, Curiel teaches a method for producing recombinant adenoviral vectors with modified fiber proteins, which includes a shuttle plasmid designed for recombination with a fiber rescue plasmid. The rescue plasmid encodes a complete copy of the adenovirus genome with the exception that the fiber gene is replaced by an origin of replication and an antibiotic resistance gene. The fiber shuttle plasmid

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has an origin of replication, an antibiotic resistance gene and an adenovirus genome fragment containing a fiber gene, which can be a modified fiber gene, and flanking sequences. The two plasmids are transfected into an appropriate cell line to allow homologous recombination to generate an adenovirus genome encoding a modified fiber protein. Curiel further teaches that the modified fiber gene can be a chimeric fiber protein consisting of the Ad5 tail and shaft domains and the Ad3 knob domain.

Curiel does not teach or suggest any isolated nucleic acid molecules containing adenovirus TPL sequences, with at least two TPL exons that are either the same or are from different adenoviruses and/or in a non-native order, operatively linked to a promoter and to adenoviral structural proteins (fiber protein). Therefore, Curiel does not cure the deficiencies of Sheay *et al.* or Kaufman.

ANALYSIS

The combination of teachings of the cited references does not result in the presently claimed subject matter

There is no teaching or suggestion in any of the cited references, singly or in any combination, to arrive at the instantly claimed subject matter. Sheay *et al.* and Kaufman teach TPL sequences from adenovirus type 2; however, neither Sheay *et al.* nor Kaufman teaches or suggests TPL sequences operatively linked to a promoter or a sequence of nucleotides encoding an adenoviral structural protein. Further, neither Sheay *et al.* nor Kaufman teaches or suggests any TPL sequences containing TPL exons that are either the same or from different adenoviruses and/or in non-native order. Curiel, directed to adenoviral vectors encoding modified adenoviral fiber genes, does not teach or suggest operatively linking the sequences encoding the fiber genes to TPL sequences containing TPL exons that are either the same or from different adenoviruses and/or in non-

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native order. Thus, Curiel does not cure the deficiencies of Sheay *et al.* or Kaufman.

Neither Sheay *et al.* nor Kaufman, directed to studying the role of TPL sequences in enhanced translational control, provides any teaching or suggestion of the desirability of enhancing adenoviral structural gene expression (such as the fiber gene expression) by operatively linking TPL sequences to a promoter and an adenoviral structural protein. Sheay *et al.* teaches the relative strengths of various promoter/enhancer (TPL sequence) combinations in enhancing translational efficiency, and Kaufman teaches that the TPL "translational control" signals may be used as an "improved means of expressing heterologous proteins," such as human proteins (page 693, col. 2). Further, none of the TPL sequences taught by Sheay *et al.* or Kaufman contain TPL exons that are either the same or from different adenoviruses and/or in non-native order.

Curiel *et al.*, directed to adenoviral vectors with altered tropism achieved by modification of the fiber protein, does not cure the deficiencies of Sheay *et al.* or Kaufman. Curiel teaches construction of fiber variants to create modified adenoviral vectors with altered tropism; Curiel does not teach or suggest obtaining enhanced expression of the fiber protein gene or any other adenoviral structural gene. There is no teaching or suggestion in any of the cited references, singly or in any combination, to obtain enhanced expression of any adenoviral structural gene, including a fiber gene. Moreover, the combination of the references does not lead to any construct containing TPL sequences whose exons are either the same or from different adenoviruses and/or in non-native order.

Since none of the cited references, singly or in combination, teaches or suggests the instantly claimed subject matter, the Examiner has failed to set forth a *prima facie* case of obviousness.

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**REJECTION OF CLAIMS 12, 13, 15-17, 20-23, 41, 47, 69 and 95-97 UNDER
35 U.S.C. §103(a)**

Claims 12, 13, 15-17, 20-23, 41, 47, 69 and 95-97 are rejected under 35 U.S.C. §103(a) as being unpatentable over Sheay *et al.* and Curiel (claims 1, 6-8 and 11) or Kaufman and Curiel (claims 1, 2, 4, 6-8 and 11) in view of Wickham *et al.* (US 5,770,442). The Office Action alleges that Sheay *et al.* and Kaufman teach adenovirus TPL sequences and Curiel teaches a plasmid encoding a chimeric fiber protein. The Office Action further alleges that Wickham *et al.* teaches the use of 293 cells, which complement the E1 region of the adenovirus genome, for transfection and stable expression of a recombinant gene to generate recombinant adenoviruses by homologous recombination.

The Office Action concludes that one of ordinary skill in the art at the time the instant application was filed would have been motivated to use the 293 cells for homologous recombination taught by Wickham *et al.* with the chimeric fiber gene of Curiel to arrive at the instantly claimed subject matter. The Office Action further alleges that one of ordinary skill in the art would have had a reasonable expectation of success for combining the complementing cell line of Wickham *et al.* and the chimeric fiber gene of Curiel. This rejection is respectfully traversed.

RELEVANT LAW

See above.

CLAIMS

Claim 12 is directed to an adenovirus vector packaging cell line, comprising:

i) a stably integrated nucleic acid molecule, comprising an adenovirus tripartite leader (TPL) nucleotide sequence, said TPL nucleic sequence comprising (a) first and second different TPL exons or (b) first, second and third

same or different TPL exons, said TPL exons selected from the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3; and

ii) an operatively-linked promoter and a nucleic acid sequence that encodes an adenovirus structural protein,

wherein the sequence of nucleotides that encodes the TPL consists essentially of a first TPL exon operatively linked to a complete second TPL exon operatively linked to a complete third TPL exon.

Dependent claims 13, 15-17, 20-23 and 69 specify particulars of TPL exon 1 (claim 13), the promoter (claim 15), the adenovirus structural protein (claims 16 and 17) and the cell line (claims 20-23 and 69).

Claims 41 and 95-97 are each directed to a method for producing an adenovirus particle comprising providing a packaging cell line wherein said packaging cell line comprises a stably integrated nucleic acid molecule. The stably integrated nucleic acid molecule comprises a sequence of nucleotides encoding an adenovirus tripartite leader (TPL). The TPL-encoding sequence of nucleotides comprises (a) first and second different TPL exons or (b) first, second and third different TPL exons. The TPL exons are selected from the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3. The cell line supports the production of a recombinant adenovirus vector genome by complementation of a deficient viral gene in said vector genome. The method further comprises producing said adenovirus particle.

Claim 41 specifies that the nucleic acid molecule is operatively linked to a promoter and operatively linked to a second nucleic acid molecule encoding an adenovirus structural protein. Dependent claim 47 specifies that the adenovirus structural protein is fiber protein.

Claim 95 specifies that the nucleic acid molecule is operatively linked to a second nucleic acid molecule encoding an adenovirus structural protein. Claim 97 specifies that the stably integrated nucleic acid molecule further comprises a sequence encoding adenovirus fiber protein.

Differences Between the Claims and the Teachings of the Cited References

Sheay *et al.*, Kaufman and Curiel *et al.*

Sheay *et al.*, Kaufman and Curiel are discussed above. None of the references, singly or in combination, teaches or suggests packaging cell lines containing with stably integrated and expressing TPL sequences and/or any adenovirus structural proteins. Sheay *et al.*, Kaufman and Curiel also do not teach or suggest any methods for producing an adenovirus particle using packaging cell lines.

Wickham *et al.* (US 5,770,442)

Wickham *et al.* teaches a method of producing recombinant adenovirus particles with chimeric fiber proteins for cell-specific targeting. Specifically, Wickham *et al.* teaches a method of producing recombinant adenoviral particles by homologous recombination in an appropriate cell line. Wickham *et al.* teaches that an appropriate cell line for producing recombinant adenovirus particles is one that expresses the receptor for the adenovirus particle produced by the described method (*i.e.*, a receptor for an adenoviral structural protein, such as fiber protein). Wickham *et al.* does not teach or suggest any packaging cell lines with stably integrated nucleic acid molecules encoding TPL sequences operatively linked to adenovirus structural proteins. Furthermore, Wickham *et al.* does not teach or suggest a method for producing an adenovirus particle using a packaging cell line with a stably integrated nucleic acid molecule encoding TPL sequences or adenovirus structural proteins.

ANALYSIS

It is respectfully submitted that the Office Action has not set forth a case of *prima facie* obviousness of the rejected claims because the combination of the cited references does not result in the claimed subject matter.

The combination of teachings of the cited references does not result in the presently claimed subject matter

As discussed above, neither Sheay *et al.*, or alternatively Kaufman, or Curiel, singly or in combination, teaches or suggests packaging cell lines with stably integrated and expressing TPL sequences operatively linked to a promoter and/or an adenovirus structural protein, or a method of producing recombinant adenovirus particles using the claimed packaging cell lines. Wickham *et al.*, which teaches a method of producing recombinant adenoviral particles by homologous recombination, does not cure these deficiencies.

As noted above, the rejected claims are directed to packaging cell lines (or methods of producing recombinant adenoviruses using the packaging cell lines), that have stably integrated TPL sequences operatively linked to a promoter and an adenovirus structural protein. Wickham *et al.* teaches a method for producing recombinant adenovirus particles by homologous recombination of a transfer plasmid and a complementing plasmid. Both plasmids are transiently transfected into cells for recombination without stable integration of either plasmid or portion thereof.

Contrary to the Examiner's assertion that Wickham *et al.* teaches transfection of cells with a recombinant gene for stable expression, Wickham *et al.* only teaches a requirement for stable expression of genes when necessary for the cell to express the receptor to the recombinant adenovirus (column 9-10). Wickham *et al.* teaches 293 cells, which stably express E1, a regulatory protein (see column 9); however, Wickham *et al.* does not teach or suggest stable integration of any adenoviral structural proteins. Furthermore, Wickham

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et al. teaches that an appropriate cell line for producing recombinant adenovirus particles may be one that expresses the receptor for the chimeric fiber (see column 12), not the fiber itself.

Sheay *et al.* or Kaufman, singly or in combination with Curiel, does not teach or suggest packaging cell lines with constructs of TPL sequences operatively linked to a promoter and a sequence of nucleotides encoding a chimeric adenovirus fiber protein. Wickham *et al.*, which also does not teach packaging cell lines containing stably integrated TPL sequences operatively linked to fiber protein, does not cure these deficiencies. Because Wickham *et al.* does not overcome the deficiencies of the combined teachings of Sheay *et al.* or Kaufman and Curiel, the Examiner has failed to set forth a *prima facie* case of obviousness.

REJECTION OF CLAIMS 98 and 99 UNDER 35 U.S.C. §103(a)

Claims 98 and 99 are rejected under 35 U.S.C. §103(a) as being unpatentable over Sheay *et al.*, Curiel and Wickham *et al.* or Kaufman, Curiel and Wickham *et al.* in view of Branellec *et al.* (US 6,410,011). The Office Action alleges that Sheay *et al.* and Kaufman teach adenovirus TPL sequences, Curiel teaches a plasmid encoding a chimeric fiber protein and Wickham *et al.* teaches a complementing cell line for generating recombinant adenoviruses by homologous recombination. The Office Action further alleges that Branellec *et al.* teaches an adenovirus comprising a suicide gene. The Office Action concludes that it would have been obvious to one ordinary skill in the art at the time the instant application was filed to combine the suicide gene of Branellec *et al.* with the adenovirus taught by the combination of Sheay *et al.*, Curiel and Wickham *et al.* or Kaufman, Curiel and Wickham *et al.* to arrive at the instantly claimed subject matter.

RELEVANT LAW

Discussed above.

CLAIMS

Claim 98 is directed to a method of producing an adenovirus particle with a genome encoding an exogenous protein. The method includes providing a packaging cell line wherein said packaging cell line comprises a stably integrated nucleic acid molecule. The stably integrated nucleic acid molecule comprises a sequence of nucleotides encoding an adenovirus tripartite leader (TPL) and an adenovirus fiber protein. The TPL-encoding sequence of nucleotides comprises (a) first and second different TPL exons or (b) first, second and third different TPL exons. The TPL exons are selected from the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3. Claim 99 further specifies that the exogenous protein is a tumor-suppressor protein or a suicide protein.

Differences Between the Claims and the Teachings of the Cited References

Sheay *et al.*, Kaufman, Curiel and Wickham *et al.*

The disclosures of Sheay *et al.*, Kaufman, Curiel and Wickham *et al.* are discussed above. None of the cited references, singly or in combination, teaches or suggests a method for producing an adenovirus particle using a packaging cell line with stably integrated TPL sequences operatively linked to a sequence encoding an adenovirus fiber protein, nor packaging cell lines containing stably integrated TPL sequences operatively linked to a sequence encoding an adenovirus fiber protein.

Branellec *et al.* (US 6,410,011)

Branellec *et al.* teaches an adenoviral vector containing a suicide gene produced by homologous recombination of a vector genome and a plasmid encoding the suicide gene. The method taught by Branellec *et al.* includes transfecting the vector genome and plasmid encoding the suicide gene into an appropriate cell line (*e.g.*, 293 cells), which complements genes deficient in the vector genome (*e.g.*, E1-E4). Furthermore, Branellec *et al.* does not teach or

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suggest packaging cell lines with stably integrated adenovirus TPL sequences operatively linked to adenovirus structural proteins.

ANALYSIS

It is respectfully submitted that the Office Action has not set forth a case of *prima facie* obviousness of the rejected claims because the combination of the cited references does not result in the claimed subject matter.

The combination of teachings of the cited references does not result in the presently claimed subject matter

As noted above, Sheay *et al.* or Kaufman, singly or in combination with Curiel and/or Wickham *et al.*, does not teach or suggest packaging cell lines with stably integrated adenovirus TPL sequences operatively linked to adenovirus structural proteins, for the production of recombinant adenovirus particles. Branellec *et al.*, directed to adenoviral vectors containing a recombinant suicide gene, also does not teach or suggest packaging cell lines with stably integrated adenovirus TPL sequences operatively linked to adenovirus structural proteins and does not cure the deficiencies of the aforementioned references. Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

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In view of the above, examination of the application on the merits is respectfully requested.

Respectfully submitted,
FISH & RICHARDSON P.C.

By:


Stephanie L. Seidman
Registration No. 33,779

Attorney Docket No. 22908-1235B
Address all correspondence to:
Stephanie L. Seidman
FISH & RICHARDSON P.C.
12390 El Camino Real
San Diego, California 92130-2081
Telephone: (858) 678-4777
Facsimile: (202) 626-7796
EMAIL: seidman@fr.com